CASE NO. 07-24(688)A

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
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Commissioner of Patents
Washington, D.C. 20231

#11
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03/12/92

APPEAL BRIEF

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

92-3627

IN RE APPLICATION OF: THOMAS F. DEUEL ET AL.

Corres. and Mail BOX AF

SERIAL NO.: 07/542,232

FILED: JUNE 21, 1990

TITLE: HEPARIN-BINDING GROWTH FACTOR

GROUP ART UNIT: 1812

EXAMINER: Shelly Guest

DATE: March 3, 1992

COMMISSIONER OF PATENTS & TRADEMARKS
WASHINGTON, D.C. 20231
Sir:

Transmitted herewith is an Appeal Brief in triplicate for filing in the above-identified application.

Fees:

[X] Appeal Brief $260.00 [37 CFR 1.17(f)]

[ ] None required (Fees paid in prior Appeal without decision on merits).

[X] In the event that an Extension of Time is required to render this paper timely filed, Appellant(s) petition(s) the Commissioner under 37 CFR 1.36(a) for an Extension of Time to respond for the period of time sufficient to render the paper transmitted herewith timely.

[X] The Commissioner is hereby authorized to charge any appropriate required fees for filing the enclosed Appeal Brief and any necessary Extension of Time to Deposit Account No. 13-4125 .

[X] A triplicate copy of this transmittal paper is enclosed.

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R02/L27/P83
R04/15/89

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Scott J. Meyer — Attorney for Applicants — 3/3/92 — Date

Registration No. 25,275

WR184
07-24(688)A

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BOX AF

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF

THOMAS F. DEUEL,
YUE-SHENG LI,
NED R. SIEGEL AND
PETER G. MILNER

SERIAL NUMBER: 07/542,232

FILED: JUNE 21, 1990

TITLE: HEPARIN-BINDING GROWTH FACTOR

Group Art Unit: 1812
Examiner: Shelly Guest

BEFORE THE BOARD
OF PATENT APPEALS
AND INTERFERENCES

92-3627

APPEAL FILED
JANUARY 27, 1992

BRIEF ON APPEAL

Hon. Commissioner of Patents and Trademarks

Washington, D. C. 20231

Dear Sir:

This is an appeal to the Board of Patent Appeals and Interferences from the decision dated October 28, 1991, of the Primary Examiner rejecting Claims 4-7 in above-identified application.

Two extra copies of this Brief and triplicate copies of a deposit account order form for charging the $260.00 filing fee to the deposit account of Monsanto Company, who is handling the prosecution of this application, are annexed hereto.

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13-4125 030 120

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on March 3 1992

Attorney for Applicants — Date 3/3/92

Registration No. 25,275

(1) STATUS OF ALL CLAIMS

Seven claims were originally filed in this application. Claims 1-3, which relate to a protein, were withdrawn from examination pursuant to a requirement for restriction. Applicant provisionally elected to prosecute the invention of Claims 4-7, which relate to DNA. Applicant's Petition to the Commissioner to reverse the restriction requirement was denied in a decision mailed December 30, 1991. In this decision the Director of Group 120 held that "the DNA and protein are patentably distinct chemical products." Accordingly, only the DNA-related Claims 4-7 are on appeal in this case. Claims 4-7 were amended by Applicant's Amendment A, filed 8/22/91, strictly in accordance with the Examiner's formal requirement that they should recite that the claimed DNA is "purified and isolated." In all other respects Claims 4-7 are in the same form as originally filed. See (7) Appendix of Claims on Appeal.

(2) STATUS OF ANY AMENDMENT FILED AFTER FINAL REJECTION

No amendments were filed after final rejection.

(3) SUMMARY OF THE INVENTION

The invention as defined in Claims 4-7 on appeal relates to novel and unobvious chemical compounds that are human and bovine DNA having sequences which encode, respectively, human and bovine heparin-binding growth factors of 18.9 kDa molecular weight in well-defined sequences of 168 amino acid residues. In

particular, Claims 4 and 5 relate to the human DNA compounds whereas Claims 6 and 7 relate to the bovine DNA compounds. The human and bovine sequences are different from each other as specifically stated at page 4, lines 20-25, of the disclosure. Thus, of the 168 amino acid residues, 163 were identical with differences existing at amino acid positions 3, 4 and 7 in the leader sequence and at amino acid positions 130 and 147 in the mature protein of the complete 168 amino acid sequence. These differences can be seen by comparing the first row of sequences in Claims 4 and 6. The amino acids in these protein sequences are shown by their conventional three-letter symbols, e.g., Met represents methionine, etc. Comparable differences exist in the DNA sequences as can be seen by comparing the sequences in Claims 5 and 7. The nucleotide bases in these DNA sequences are shown by their conventional single letter symbols, e.g., A, G, C and T which represent adenine, guanine, cytosine and thymine, respectively. Claims 4 and 6 are generic in that they include variations in the nucleotide codons (three successive nucleotides or triplets) to account for the well-known degeneracy of the genetic code. That is, many amino acids are specified by more than one codon, although there is only one methionine codon, namely ATG.

In accordance with the invention, the heparin-binding growth factor DNA compounds claimed in Claims 4-7 were purified and isolated in a form which did not exist heretofore in nature from bovine uterus and human placenta starting materials as described at page 4, lines 5-19, of the disclosure. For convenience, the heparin-binding growth factor is abbreviated "HBGF-8." The bovine HBGF-8 DNA was isolated from a bovine uterus cDNA library using the bovine N-terminal 25 amino acid sequence clone as a probe. This N-terminal sequence is shown at page 3, lines 8-10, of the disclosure. The human HBGF-8 DNA was isolated from a human

placenta cDNA library using bovine HBGF-8 cDNA fragment as a probe.

The term "heparin-binding" is based on the finding that the HBGF-8 binds tightly to Heparin-Sepharose resin as stated at page 3, lines 11-12, of the disclosure. The term "growth factor" is based on the finding that the HBGF-8 has activity as an acidic growth factor in mitogenic assay systems as stated at page 3, lines 14-18.

The importance and significance of the invention is illustrated by the fact that the bovine uterus HBGF-8 purification and isolation resulted in separation of the 18.9 kDa HBGF-8 from the 17.5 kDa bovine uterus basic fibroblast growth factor (bFGF) as stated at page 3, lines 19-31. Thus, the claimed DNA was purified and isolated in a useful and practical form which did not exist in nature.

(4) STATEMENT OF ISSUES PRESENTED FOR REVIEW

The single issue presented for review in this appeal is as follows:

- Whether Claims 4-7 are unpatentable under 35 U.S.C. §103 over Bohlen (EP 326,075) or Rauvala (EMBO J. 1989) in view of Maniatis et al. (Molecular Cloning: A Laboratory Manual).

(5) GROUPING OF CLAIMS

The claims do not stand or fall together. Claims 4 and 5, which relate to human HBGF-8 DNA, are separately patentable from Claims 6 and 7, which relate to bovine HBGF-8 DNA. Although both the human and bovine species are mammalian, the corresponding HBGF-8 DNA sequences nevertheless have fundamentally different structures. The differences in sequences have been pointed out in Part (3), Summary of the Invention. Neither sequence is obvious from the other.

Likewise, Claims 5 and 7, which recite specific DNA sequences, are separately patentable from Claims 4 and 6, which more broadly recite DNA sequences that encode the corresponding protein sequences. As pointed out in Part (3), Summary of the Invention, Claims 4 and 6 are generic in that they include variations in the nucleotide codons (three successive nucleotides or triplets) to account for the degeneracy in the genetic code. That is, many amino acids are specified by more than one codon, although there is only one methionine codon, namely ATG.

Furthermore, Claims 5 and 7 are separately patentable from each other in that the claimed sequences have substantially different lengths, they have substantially different terminal sequences and are otherwise substantially different from each other. Neither sequence is obvious from the other.

(6) THE ARGUMENT

Appellant respectfully submits that the Examiner's final rejection under 35 U.S.C. §103 on the basis of Bohlen or Rauvala in view of Maniatis is neither factually nor legally supportable and, therefore, should be reversed. Appellant's reasons for

reversal, including authorities and parts of the record relied upon, are set forth in the following argument. As will be shown in this argument, the rejection should be reversed because (I), Claims 4-7 are unobvious over the cited art since that art contains not a single iota of disclosure of any part of the DNA compounds of said claims; (II), the rejection under 35 U.S.C. §103 should be reversed because it is based on an improper combination of primary and secondary references; and (III), the rejection under 35 U.S.C. §103 should be reversed because the references, even if for the sake of argument are considered as properly combined, do not teach appellant's claimed DNA compounds but teach, instead, other DNA compounds having no homology to appellant's DNA compounds.

I. CLAIMS 4-7 ARE UNOBVIOUS OVER THE CITED ART BECAUSE THAT ART CONTAINS NOT A SINGLE IOTA OF DISCLOSURE OF ANY PART OF THE DNA COMPOUNDS OF SAID CLAIMS

As has already been stated by the Director of Group 180 in the decision on the Petition to reverse the restriction requirement, "the DNA and protein are patentably distinct chemical products." On the one hand, Claims 4-7 on appeal relate solely to DNA, not to protein. On the other hand, each of the primary references, Bohlen and Rauvala, relate to protein, not to DNA. As a matter of fact, there is not so much as one iota of disclosure in either of these primary references which deals with DNA compounds. Thus, these references are completely non-relevant to appellant's patentably distinct Claims 4-7. The Examiner has

not even pointed out a single word in either of these primary references which relates to DNA compounds.

That the primary references are non-relevant to appellant's invention is self-evident from the fact that they are not even concerned with the general field of molecular biology to which appellant's invention is directed. Thus, a careful reading of Bohlen will reveal that it merely describes an in vitro method of isolating a brain mitogen from bovine brain. There is not one word or iota within the four corners of the reference which concerns a DNA compound, let alone appellant's claimed DNA compounds.

Likewise, a careful review of Rauvala will reveal that it also merely describes an in vitro method of isolating a brain mitogen, but from rat brain instead of bovine brain as in Bohlen. But as in Bohlen, so too in Rauvala, there is not one word or iota within the four corners of the reference which concerns a DNA compound, let alone appellant's claimed DNA compounds.

Clearly then, the Examiner has cited two primary references drawn from the protein art which is irrelevant to the patentably distinct DNA Claims 4-7 here on appeal.

Although the secondary reference, Maniatis, refers to DNA cloning, it has nothing whatsoever to do with appellant's novel and unobvious DNA compounds. Thus, Maniatis is nothing more than a state-of-the-art treatise on the principles and techniques, i.e. methods, of gene cloning. However, none of appellant's Claims 4-7 relate to a method of gene cloning. Instead, they relate to novel and unobvious DNA compounds. That is, appellant's claims recite novel and unobvious chemical products; they do not recite a method of cloning such as disclosed by

Maniatis. To reject appellant's claims to novel and unobvious chemical compounds on the basis of a laboratory textbook which merely describes general methods for molecular cloning without any disclosure of appellant's claimed chemical compounds themselves is as improper and invalid as it would be to reject the product claims to a novel and unobvious pharmaceutical compound on the basis of a laboratory textbook which merely describes general techniques for organic synthesis of chemical compounds without any disclosure of the claimed compound or compounds that are homologous to the claimed compound. It is axiomatic that in order for a reference to be a valid reference against claims to a chemical compound that reference must disclose a teaching of the structure of the of the claimed chemical compound or compounds homologous thereto, and not merely methods or techniques for making chemical compounds in general without any relationship to the structure of the claimed compounds. Both the structure and properties of the compound must be considered under 35 U.S.C. 103. See, e.g., In re Papesch, 137 USPQ 43 (CCPA 1963). The only DNA compound shown in the cited pages of the Maniatis reference is a 902 bp DNA of πVX shown on page 353. However, the Examiner has failed to point out any homology whatsoever, not even the slightest homology, between the Maniatis 902 bp DNA compound of πVX and appellant's claimed HBGF-8 DNA compounds. It is manifestly evident that the reason the Examiner has failed to point out any homology is that there clearly is no such homology. Appellant's DNA and the DNA shown in the reference are as different from each other as night and day are different from each other. The Examiner has thus come up with a complete "blank" so far as finding any teaching of appellant's claimed chemical products. Most certainly, the Maniatis reference provides no support for the rejection of Claims 4-7 under 35 U.S.C. §103.

II. THE REJECTION UNDER 35 U.S.C. §103 SHOULD BE REVERSED BECAUSE IT IS BASED ON AN IMPROPER COMBINATION OF PRIMARY AND SECONDARY REFERENCES

As has already been pointed out in Argument I, above, the primary references, Bohlen and Rauvala, relate only to methods of in vitro purification of heparin-binding growth factors from brain cells, they provide no teaching whatsoever concerning DNA compounds; whereas, the secondary reference, Maniatis, relates only to general methods of gene cloning in which the only DNA compound shown is a 902 bp DNA of πVX, it provides no teaching whatsoever concerning purification of heparin-binding growth factors from brain cells. Thus, it is manifestly evident that there is no valid basis for combining these references because they relate to two entirely different types of subject matter. That is, in making the rejection under Section 103, the Examiner has combined unrelated and non-analogous art in which no suggestion or teaching for appellant's combination can be found in the art itself. The Examiner's conclusion on obviousness ignores the fact that nothing in the cited references themselves suggests the combination. The approach used by the Examiner is at odds with the long-accepted principle of patent law that:

> "the mere fact that those disclosures can be combined does not make the combination obvious unless the art also contains something to suggest the desirability of the combination." In re Imperato, 179 USPQ 730, 732 (CCPA 1973); In re Bergel, 130 USPQ 206 (CCPA 1961).

As further stated by the Court of Customs and Patent Appeals in In re Regel et al, 188 USPQ 136, 139 (CCPA 1975):

> "there must be some logical reason apparent from positive concrete evidence of record which justifies a combination of primary and secondary references."

It is respectfully submitted that the Examiner's conclusion on Section 103 obviousness is not supported by any positive, concrete evidence in these references. Instead, it is believed that the Examiner has merely used hindsight analysis in making the combination after reading appellant's disclosure. That is, it is apparent that in the instant case the Examiner, after reading appellant's disclosure, has used hindsight analysis and pieced together the unrelated primary and secondary references not in a manner suggested by the art itself but, rather, in a manner such as to obtain appellant's invention. As consistently held by the patent courts:

> "such a hindsight analysis, however, is not allowed by 35 USC 103." In re Linnert and Espy, 135 USPQ 307, 311 (CCPA 1962).

See also, ACS Hospital Systems, Inc. vs. Montefiore Hospital, 221 USPQ 929, 933 (Fed. Cir. 1984); and In re Fine, 5 USPQ2d 1597, 1599-1600 (Fed. Cir. 1988), where the CAFC refers to "the insidious effect of the hindsight syndrome." In order to make such a finding of obviousness in appellant's particular claimed DNA compounds, it is incumbent upon the Examiner to support the combination of references by specifically pointing out where the suggestions for such combination to arrive at appellant's claimed DNA compounds occurs in the references themselves. No such suggestions can be found in the references and the Examiner has not pointed out any. Instead, the Examiner, in the final rejection, Paper No. 7, at page 3, has merely concluded in a rather cavalier manner that "it would have been entirely obvious to attempt to isolate a known protein from different tissue types and even different species... [and] it would have been obvious to

clone the instant gene sequence since the cloning procedures are used only in a manner taught by the prior art for the purposes taught by the prior art (emphasis added)." Such broad brush conclusionary statements not only fail to point out any suggestion or teaching in the art itself for making the combination of references, but they also are based on several other improper approaches to examination for patentability under 35 U.S.C. §103. Thus, the Examiner's conclusion that it would have been obvious "to attempt to isolate a protein from different tissue types" is tantamount to saying that appellant's invention is merely a matter of choice and that it would be obvious to try what appellant has done. However, that is not an appropriate basis for rejecting an applicant's claims. As stated by the Board of Appeals in the case of In re Haas et al, 144 USPQ 98 (PTO Bd. App. 1964), "It is not a matter of choice presented by the prior art." No motivation in the art exists for doing what appellant has done. It has been consistently held by the Court of Customs and Patent Appeals and the Court of Appeals for the Federal Circuit that "obvious to try" is irrelevant to the Section 103 test of obviousness. See, e.g., In re Tomlinson et al., 150 USPQ 623 (CCPA 1963); and In re Antonie 195 USPQ 6, 8 (CCPA 1977), in which the CCPA said:

> "...overemphasis on the routine nature of the data gathering to arrive at appellant's discovery, after its existence became expected, overlooks the last sentence of §103. In re Saether, 181 USPQ 36 (CCPA 1974)."

See also In re Lindell, 155 USPQ 521, 523 (CCPA 1967), in which the CCPA held that:

> "...application of the 'obvious to try' test would often deny patent protection to inventions growing out of well-planned research which is, of course guided into those areas in which success is deemed most likely...".

See also In re Goodwin et al, 198 USPQ 1, 3 (CCPA 1978), in which the CCPA held as follows:

> "Disregard for the unobviousness of results of 'obvious to try' experiments disregards the 'invention as a whole' concept of §103...".

The rule against the use of "obvious to try" concept under 35 U.S.C. §103 has been followed by the CAFC. See, e.g., In re Geiger, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987); In re Dow Chemical Co., 5 USPQ2d 1529, 1532 (Fed. Cir. 1988); In re Fine, 5 USPQ2d 1597, 1598 (Fed. Cir. 1988).

Moreover, the Examiner's conclusion that it would have been obvious to attempt "to isolate a protein" has no relevance to the claimed invention. As already pointed out, above, appellant's claims are not directed to a method of isolating a protein; in fact, they are not even directed to a method of isolating DNA or anything else. Instead, they are directed to novel chemical compounds. The Examiner's conclusion thus is completely misdirected to something that is not being claimed.

Furthermore, the Examiner's conclusion completely ignores the point made by the Director of Group 120 that the DNA claims are patentably distinct from the protein claims. If anything, the Examiner's conclusions on a method of isolating a protein may possibly be apropos to protein claims which have been withdrawn from examination by the Examiner but, most certainly, they are not apropos to the DNA chemical compound claims. The Examiner's conclusion is based on a completely contorted and inconsistent approach to Examination of chemical compound claims under the mandate of 35 U.S.C. §103. The Examiner has completely confused the instant issue of patentability of novel chemical compounds under Section 103 with the issue of patentability of a method of

isolation of chemical compounds, which is a non-issue in this appeal.

Likewise, the Examiner's conclusion that it would have been obvious "to clone the instant gene sequence since the cloning procedures are used in the manner taught by the prior art" has no relevance to the claimed invention. As already pointed out, above, appellant's claims are not directed to procedures for cloning; instead, they are directed to novel DNA chemical compounds. The Examiner's conclusion thus is completely misdirected to something that is not being claimed.

III. THE REJECTION UNDER 35 U.S.C. §103 SHOULD BE REVERSED BECAUSE THE REFERENCES EVEN IF PROPERLY COMBINED DO NOT TEACH APPELLANT'S INVENTION

As pointed out in Argument II, above, the rejection under 35 U.S.C. §103 should be reversed because it is based on an improper combination of references. But assuming for the sake of argument that the Board concludes that the references are properly combined, then the rejection should nevertheless still be reversed because the combination does not teach appellant's claimed invention for reasons as follows:

First of all, appellant's claimed DNA is purified and isolated from entirely different biological sources than the protein materials of Bohlen and Rauvala. Thus, on the one hand, appellant purified and isolated the DNA from bovine uterus and human placenta; whereas, on the other hand, Rauvala isolated and purified his protein from rat brain, and Bohlen isolated his protein from bovine brain (and also suggested rat and chicken

brains). That is, both Bohlen and Rauvala emphatically teach the use of brain tissue as a source of isolating a protein. This is an entirely different tissue than used as a source of appellant's DNA. There is nothing in the four corners of these references which teaches or suggests the use of bovine uterus or human placenta as a source of appellant's HBGF-8 DNA. Instead of pointing out anything in these references, the Examiner has merely concluded in a rather cavalier manner that "it would be obvious to attempt to isolate a known protein from different tissue types...(emphasis added)." This conclusion is fallacious for at least two sound reasons: (a) it fails to point out why it would be obvious to mentally hurdle from the three brain sources emphasized by the references (rat, chicken and bovine brains) for the isolation of a protein to the uterus and placenta sources used by appellant for the isolation of DNA, and (b) it fails to provide any evidence that appellant's claimed DNA is a "known" compound.

Moreover, there is no apparent physiological relationship between the brain on the one hand and the uterus and placenta on the other hand. There is absolutely nothing in the references cited by the Examiner which supports the conclusion that it would be obvious to attempt to isolate from the uterus or placenta some particular compound found in the brain. The body has many other tissues, e.g., liver, kidney, heart, pancreas, lungs, bone, skin, etc. But in each instance of the rat, chicken and bovine, the references teach only the brain.

Secondly, it is absolutely fallacious for the Examiner to reason that appellant has merely isolated a known protein. Of course, whether or not appellant's protein was known is irrelevant to the claims in issue which concern DNA, not the protein claims which were withdrawn from examination by the

Examiner as being drawn to a patentably distinct invention. Nevertheless, even with respect to appellant's protein the Examiner has pointed to nothing in the prior art which establishes that it is a known protein. The facts are otherwise because, subsequent to the filing date of appellant's application, publication was made by Rauvala which clearly supports the conclusion that appellant's protein was unknown and different from the Rauvala protein. Thus, in the Second Supplemental Information Disclosure Statement filed by appellant on January 7, 1991, the Examiner's attention was called to Rauvala, J. Biol. Chem. 265, 16721-16724 (1990). Although the latter publication is not prior art since it has a publication date subsequent to appellant's filing date as well as subsequent to the priority filing date of appellant's parent application, it can be seen from the fully disclosed rat brain-derived protein sequence of Rauvala that both the bovine uterus- and human placenta-derived sequences of appellant are significantly different from the rat brain sequence of Rauvala. This confirms that appellant's claimed DNA is not a known compound as erroneously alleged by the Examiner. For the convenience of the Board, appellant attaches hereto as Exhibit A an enlarged copy of the Rauvala sequence of FIG. 2 on page 16722, in which appellant's amino acid residues and nucleotides which differ from Rauvala are highlighted. In appellant's HBGF-8 from human placenta the sequences differ at amino acid residues 98, -13, -30 and -31. In appellant's HBGF-8 from bovine uterus the sequences differ at amino residues -13, -29, -30 and -31. Thus, the Rauvala rat brain protein has Asp at position 98, whereas appellant's human placenta-derived HBGF-8 has Glu at the corresponding residue (residue 130 in appellant's sequence). Likewise, Rauvala's rat brain protein has Ser-Ser in residues -30 and -31, whereas appellant's human placenta-derived HBGF-8 has Gln-Ala at the corresponding residues (residues 2 and 3 in

appellant's sequence). Since appellant's claimed DNA includes coding for the signal peptide, appellant's amino acid numbering starts with the NH_2 terminal Met as number +1. Since the Bohlen reference discloses only the first 19 residues of his NH_2 terminal sequence of rat brain protein and no signal sequence is provided, no full comparison can be made with appellant's sequence. However, since Bohlen's protein is isolated from brain tissue as is the Rauvala protein, it is reasonable to assume that it is more similar to the Rauvala protein than it is to appellant's compounds which are derived not from brain tissue, but from uterus and placenta tissue. But irrespective of what is speculatively concluded from Bohlen, it is manifestly evident that it teaches nothing whatsoever concerning appellant's claimed DNA chemical structure. Speculation and opinion of the Examiner cannot be substituted for factual differences between what "may be properly noted in any portion of a claim" and what "must be included within the basis for comparison with the prior art if we are to properly evaluate the differences between the invention defined in a claim and the teachings of a reference." In re Duva, 156 USPQ 90, 94 (CCPA 1967).

In view of the foregoing arguments, it is respectfully submitted that the rejection of Claims 4-7 be reversed.

Respectfully submitted,

By _____
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March 3, 1992

(7) APPENDIX OF CLAIMS ON APPEAL

4. A purified and isolated DNA sequence consisting of a sequence encoding human heparin binding growth factor of 168 amino acids having the following amino acid sequence:

Met Gln Ala Gln Gln Tyr Gln Gln Arg Arg Lys Phe Ala Ala	15
Ala Phe Leu Ala Phe Ile Phe Ile Leu Ala Ala Val Asp The Ala	30
Glu Ala Gly Lys Lys Glu Lys Pro Glu Lys Lys Val Lys Lys Ser	45
Asp Cys Gly Glu Trp Gln Trp Ser Val Cys Val Pro Thr Ser Gly	60
Asp Cys Gly Leu Gly Thr Arg Glu Gly Thr Arg Thr Gly Ala Glu	75
Cys Lys Gln Thr Met Lys Thr Gln Arg Cys Lys Ile Pro Cys Asn	90
Trp Lys Lys Gln Phe Gly Ala Glu Cys Lys Tyr Gln Phe Gln Ala	105
Trp Gly Glu Cys Asp Leu Asn Thr Ala Leu Lys Thr Arg Thr Gly	120
Ser Leu Lys Arg Ala Leu His Asn Ala Glu Cys Gln Lys Thr Val	135
Thr Ile Ser Lys Pro Cys Gly Lys Leu Thr Lys Pro Lys Pro Gln	150
Ala Glu Ser Lys Lys Lys Lys Lys Glu Gly Lys Lys Gln Glu Lys	165
Met Leu Asp	168

5. The purified and isolated cDNA of human heparin-binding growth factor having the following nucleotide sequence:

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GTCAAAGGCA GGATCAGGTT CCCCGCCTTC CAGTCCAAAA ATCCCGCCAA     50
GAGAGCCCCA GAGCAGAGGA AAATCCAAAG TGGAGAGAGG GGAAGAAAGA    100
GACCAGTGAG TCATCCGTCC AGAAGGCGGG GAGAGCAGCA GCGGCCCAAG    150
CAGGAGCTGC AGCGAGCCGG GTACCTGGAC TCAGCGGTAG CAACCTCGCC    200
CCTTGCAACA AAGGCAGACT GAGCGCCAGA GAGGACGTTT CCAACTCAAA    250
AATGCAGGCT CAACAGTACC AGCAGCAGCG TCGAAAATTT GCAGCTGCCT    300
TCTTGGCATT CATTTTCATA CTGGCAGCTG TGGATACTGC TGAAGCAGGG    350
AAGAAAGAGA AACCAGAAAA AAAAGTGAAG AAGTCTGACT GTGGAGAATG    400
GCAGTGGAGT GTGTGTGTGC CCACCAGTGG AGACTGTGGG CTGGGCACAC    450
GGGAGGGCAC TCGGACTGGA GCTGAGTCCA AGCAAACCAT GAAGACCCAG    500
AGATGTAAGA TCCCCTGCAA CTGGAAGAAG CAATTTGGCG CGGAGTGCAA    550
ATACCAGTTC CAGGCCTGGG GAGAATGTGA CCTGAACACA GCCCTGAAGA    600
CCAGAACTGG AAGTCTGAAG CGAGCCCTGC ACAATGCCGA ATGCCAGAAG    650
ACTGTCACCA CTCCCAAGCC CTGTGGCAAA CTGACCAAGC CCAAACCTCA    700
AGCAGAATCT AAGAAGAAGA AAAAGGAAGG CAAGAAACAG GAGAAGATGC    750
TGGATTAAAA GATGTCACCT GTGGAACATA AAAAGGACAT CAGCAAACAG    800
GATCAGTTAA CTATTGCATT TATATGTACC GTAGGCTTTG TATTCAAAAA    850
TTATCTATAG CTAAGTACAC AATAAGCAAA AACAAAAAGA AAAAAAAAAA    900
AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA    950
AAAAAAAAAA A                                              961
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6. A purified and isolated DNA sequence of a sequence encoding bovine heparin binding growth factor of 168 amino acids having the following amino acid sequence:

Met Gln Thr Pro Gln Tyr Leu Gln Gln Arg Arg Lys Phe Ala Ala 15
Ala Phe Leu Ala Phe Ile Phe Ile Leu Ala Ala Val Asp The Ala 30
Glu Ala Gly Lys Lys Glu Lys Pro Glu Lys Lys Val Lys Lys Ser 45
Asp Cys Gly Glu Trp Gln Trp Ser Val Cys Val Pro Thr Ser Gly 60
Asp Cys Gly Leu Gly Thr Arg Glu Gly Thr Arg Thr Gly Ala Glu 75
Cys Lys Gln Thr Met Lys Thr Gln Arg Cys Lys Ile Pro Cys Asn 90
Trp Lys Lys Gln Phe Gly Ala Glu Cys Lys Tyr Gln Phe Gln Ala 105
Trp Gly Glu Cys Asp Leu Asn Thr Ala Leu Lys Thr Arg Thr Gly 120
Ser Leu Lys Arg Ala Leu His Asn Ala Asp Cys Gln Lys Thr Val 135
Thr Ile Ser Lys Pro Cys Gly Lys Leu Thr Lys Ser Lys Pro Gln 150
Ala Glu Ser Lys Lys Lys Lys Lys Glu Gly Lys Lys Gln Glu Lys 165
Met Leu Asp 168

7. The purified and isolated cDNA of bovine heparin-binding growth factor having the following nucleotide sequence:

GAGTGGAGAG AGTAGAAGAA AGAGAGCAGG GAGTCACCGG GCGTGCGGGG 50

GCGGAGAGCA GCGGCCGCCG CGAGCACCAG CGACTTGGGT ACCTGGACTC 100

AGGGCAGAAA AACCTCTCCC GGATCAACAA AGGCAGCCTG AGCGCGCACC 150

GCTCTTTTGC GACTCCAAAA TGCAGACTCC ACAGTACCTG CAGCAACGTC 200

GAAAATTTGC AGCTGCCTTT TTGGCATTTA TTTTCATCTT GGCAGCTGTG 250

GACACCGCTG AAGCAGGAAA GAAAGAGAAA CCAGAAAAGA AGGTGAAGAA 300

GTCTGACTGT GGAGAATGGC AGTGGAGTGT GTGTGTACCA ACCAGTGGGG 350

ACTGTGGGCT GGGCACCCGC GAGGGCACCC GTACCGGAGC TGAGTGTAAA 400

CAAACCATGA AGACCCAGAG ATGTAAGATC CCCTGCAACT GGAAAAAGCA 450

ATTTGGAGCG GAGTGCAAAT ACCAGTTCCA GGCCTGGGGA GAATGTGATC 500

TGAACACGGC TCTGAAGACC CGAACTGGGA GCCTGAAGCG AGCCCTCCAC 550

AACGCCGACT GCCAGAAGAC AGTCACCATC TCCAAGCCCT GTGGCAAGCT 600

GACCAAGTCC AAACCTCAAG CAGAATCTAA GAAGAAGAAA AAGGAAGGCA 650

AGAAACAGGA GAAGATGCTG GACTAAAAGC CACCACCTTC CGTGGACCAT 700

GAAAAGGACA TCAGCAAACA CGATCAGTTA ACTATTGCAT TTATATCTAC 750

CGTAGGCTTT TTATTCAAAA ATTATCTATA GCTTAAGTAC ACAATAGGCA 800

GAAACAAAAT GAAAAGAAAA ATTTTGTAGT AGCATTTTTT TTAAATGTAT 850

CAATATACCA TAGTACCACT AGGGACTTAT AATAGAGGAC TGTAATCCTA 900

TTTAGAATGT TGACTTATAG TACATGTTAA GTGATAGAAA ACTGAGGTAA 950

GTTTTTTGAA GTTATGTGAT ATTTTACATT ACATTTTTTT TTACATTTTT 1000

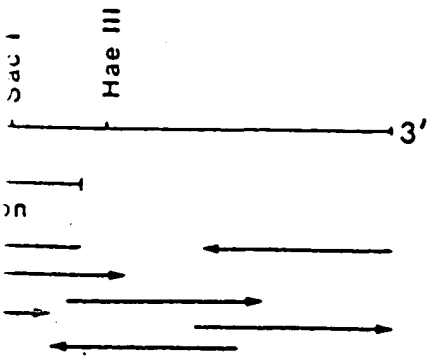
TTCTTTTGGC AGCAATTTAA ATGTTATGAC TATGTAAACT ACTTCTCTTG 1050

TTAGGTAATT TTTTTCACCT AGACTTTATT TCCCAATTGA GAAAAATATC 1100

TACTAAACAA AGCAGCAATA AAATATGATC ATCCTATCTG AGGAAAATAT 1150

CTCTTTTTCT GCCAGTGGAT TTTTAAAAAA TTGTAGTCAA CAAAAT 1196

EXHIBIT 1



ıse map and sequencing strat-
ıdes rat brain HB-GAM. The
-GAM was obtained as described
Arrows indicate the direction and

ıreparations used for Northern
RNAs were transferred from the
ɔn filter (Hybond-N, Amersham
. clone that contained the whole
with ^{32}P (the oligolabeling kit of
ıe filters. The filters were washed
(two times for 20 min at room
SC followed by two times for 15
. SSC (1 × SSC = 0.15 M NaCl,

–Anti-synthetic peptide antibod-
·quence of HB-GAM have been
;AM antibodies were raised in a
protein (3) in complete Freund's
; injections. A booster injection
ete Freund's adjuvant was given
ɔsters were given with 2–3-week
nity-purified (3) with 0.5 mg of
Affi-Gel 10 gel (Bio-Rad). For
were immediately solubilized in
ntaining 1 mM phenylmethylsul-
The samples were run on 5–20%
.ransferred to nitrocellulose (10),
lescribed in detail elsewhere (3).
in Western blotting were located
:d anti-rabbit IgG (Bio-Rad).

DISCUSSION

–Fig. 1 shows the restriction
y for the cDNA that encodes
ere isolated; the longer clone
rter one 750 bp. The longer
-untranslated region and 474
(Fig. 2). The 5′-untranslated
ebrate mRNA; about 20% of
und to contain mRNA leader

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1                                                GACAGAACGGAATTGAGTGAAGGCAGGATCAGGTTCCCCG          40

41   CCTTCCCGTCCAAAAATCCCGCCAAGGAAGCCCCAGAGCACAAGAAAATCCAAAGTGGAGGCA          104

105  GGGGAAGAAAGAAAGCACTCAGTCATCCATCCAGAAGGGGGGAGAGCGCAGCCGCCCAGGCAG          167

168  GAGCAGCAGCCAGCGATACCTGGAGTCCGTTGCAGAAACCTCGCCCTGCACTTTGCAACAAAG          230

231  GCAGCCTGCTGTCAGCGAGGACATCTGCCAAGCCAAAAA ATG TCG TCC CAG CAA TAC    287
-32                                          Met Ser Ser Gln Gln Tyr    -27

288  CAG CAG CAA CGT CGA AAA TTT GCA GCT GCC TTC CTG GCT TTG ATT TTC    335
-26  Gln Gln Gln Arg Arg Lys Phe Ala Ala Ala Phe Leu Ala Leu Ile Phe    -11

336  ATC CTG GCA GCC GTG GAC ACT GCT GAG GCC GGG AAA AAA GAG AAA CCA    383
-10  Ile Leu Ala Ala Val Asp Thr Ala Glu Ala Gly Lys Lys Glu Lys Pro    +6

384  GAA AAA AAG GTG AAA AAA TCT GAC TGT GGA GAA TGG CAA TGG AGT GTG    431
 7   Glu Lys Lys Val Lys Lys Ser Asp Cys Gly Glu Trp Gln Trp Ser Val    22

432  TGC GTG CCC ACC AGC GGG GAC TGT GGT CTA GGC ACC CGG GAG GGC ACT    479
 23  Cys Val Pro Thr Ser Gly Asp Cys Gly Leu Gly Thr Arg Glu Gly Thr    38

480  CGC ACT GGT GCC GAG TGC AAA CAA ACC ATG AAG ACT CAG AGA TGT AAG    527
 39  Arg Thr Gly Ala Glu Cys Lys Gln Thr Met Lys Thr Gln Arg Cys Lys    54

528  ATC CCT TGC AAC TGG AAG AAG CAG TTT GGA GCT GAG TGC AAA TAC CAG    575
 55  Ile Pro Cys Asn Trp Lys Lys Gln Phe Gly Ala Glu Cys Lys Tyr Gln    70

576  TTC CAG GCT TGG GGA GAA TGT GAC CTC AAT ACC GCC TTG AAG ACC AGA    623
 71  Phe Gln Ala Trp Gly Glu Cys Asp Leu Asn Thr Ala Leu Lys Thr Arg    86

624  ACT GGC AGT CTG AAG AGA GCT CTG CAC AAT GCC GAC TGT CAG AAA ACT    671
 87  Thr Gly Ser Leu Lys Arg Ala Leu His Asn Ala Asp Cys Gln Lys Thr   102

672  GTC ACC ATC TCC AAG CCC TGT GGC AAA CTC ACC AAG CCC AAG CCT CAA    719
103  Val Thr Ile Ser Lys Pro Cys Gly Lys Leu Thr Lys Pro Lys Pro Gln   118

720  GCG GAA TCA AAG AAG AAG AAA AAG GAA GGC AAG AAA CAG GAG AAG ATG    767
119  Ala Glu Ser Lys Lys Lys Lys Lys Glu Gly Lys Lys Gln Glu Lys Met   134

768  CTG GAT TAAAAGAGGCCACCTTTTGTGGACAAGGAAAAGGACATCAGCAAGCAGGATCAGT    828
135  Leu Asp  *                                                       136

829  TAACTATTACATTTATACCTACTGTAGGCTTTTTATTCAACAGTTATCTGTAGCTTAAGTACA    891

892  TGATAGGCAAAAACAAAGAGAAAAGAAATGTTTTTGTAGTAGCATTTTTTTAATGTATACCAT    954

955  AGTACCAGTAGGGGTTTATAAATAAAGGACTGTAATACTATTTAGGAAGTTGAGTTGTAGTACA   1017

1018 TGATAGATGGTAGGATTGAGGTAAGTTTTTTTTTTTTGTTTTTGTTTTGTTTTGGTTTTGGTT   1080

1081 TGTTTTGCTTTTCAAAGTTATGTGATATTTCACATTTAAATCTTTTTTTTTACATTTCCAAAC   1143

1144 CTTGTGCATCAATTTAAATGTTACAACCATGTAAACTACTTCCCTTATTAGATAGATTTTCAC   1206

1207 CTAGACTTTTTTTTCCCAATTCAGAAGAAAATATACACTAA                          1247
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FIG. 2. **The nucleotide and predicted amino acid sequences of rat brain HB-GAM.** The nucleotides are listed in the 5′ to 3′ direction. The termination site is marked with *. Amino acid residues are *numbered negative* within the signal sequence that is *double underlined*. Amino acid sequences obtained from protein sequencing are *underlined*. Except for the CNBr fragment (residues 49–52 that were read as *X*-Thr-Gln-Arg), these were obtained from N-terminal sequencing and from endoproteinase Lys-C fragments.

for defining the cleavage site (12, 13). According to this rule a small uncharged amino acid is invariably found at positions −3 and −1. A common amino acid at these locations is alanine, which is found at −3 and −1 in the HB-GAM precursor (Fig. 2). Further evidence that this area actually defines the cleavage site comes from the finding that the mature protein starts from the ensuring N-terminal sequence (3).

The occurrence of the signal peptide that is characteristic of secretory proteins agrees with the previous findings on the cellular distribution of the protein. HB-GAM was detected by